US009326980B2

(12) **United States Patent**
Hamidi

(10) **Patent No.:** **US 9,326,980 B2**
(45) **Date of Patent:** ***May 3, 2016**

(54) **METHOD AND SYSTEM FOR SYNTHESIZING NANOCARRIER BASED LONG ACTING DRUG DELIVERY SYSTEM FOR BUPRENORPHINE**

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/336,975**

(22) Filed: **Jul. 21, 2014**

(65) **Prior Publication Data**

US 2015/0024033 A1 Jan. 22, 2015

(51) **Int. Cl.**
　　*A61K 9/127* (2006.01)
　　*A61K 31/485* (2006.01)
　　*A61K 9/00* (2006.01)

(52) **U.S. Cl.**
　　CPC ............. *A61K 31/485* (2013.01); *A61K 9/0019* (2013.01); *A61K 9/1271* (2013.01); *A61K 9/1277* (2013.01); *Y10S 514/812* (2013.01); *Y10S 977/773* (2013.01); *Y10S 977/906* (2013.01); *Y10S 977/907* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

The embodiments herein provide a nano-carrier system for delivering a long-acting injectable drug of buprenorphine and a method of synthesizing the same. The buprenorphine entrapped nanoparticles are prepared using a lipid/phospholipid core which is coated by a polymer. The lipid and phospholipid are dissolved in organic solvent. This solution is transferred into an aqueous phase consisting of distilled water or a buffer. A solution of polymer is added drop wise. The drug entrapped nanoparticle formation is achieved by diffusion of the organic solvent within the aqueous solvent to obtain the nanoparticles. The drug gets entrapped within the nanoparticles via the anti-solvency effect of the aqueous matrix. The resulting drug nanocarriers are capable of releasing the drug in a slow rate upon injection. The synthesized drug carrying nanoparticles are cryopreserved stored for future administration. For better storage, the nanodispersion is dried to form a powder.

**6 Claims, 7 Drawing Sheets**



Size Distribution Report by Intensity
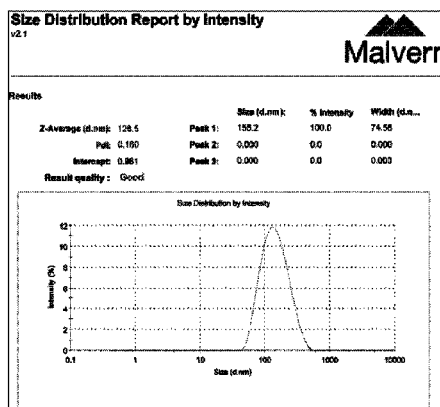
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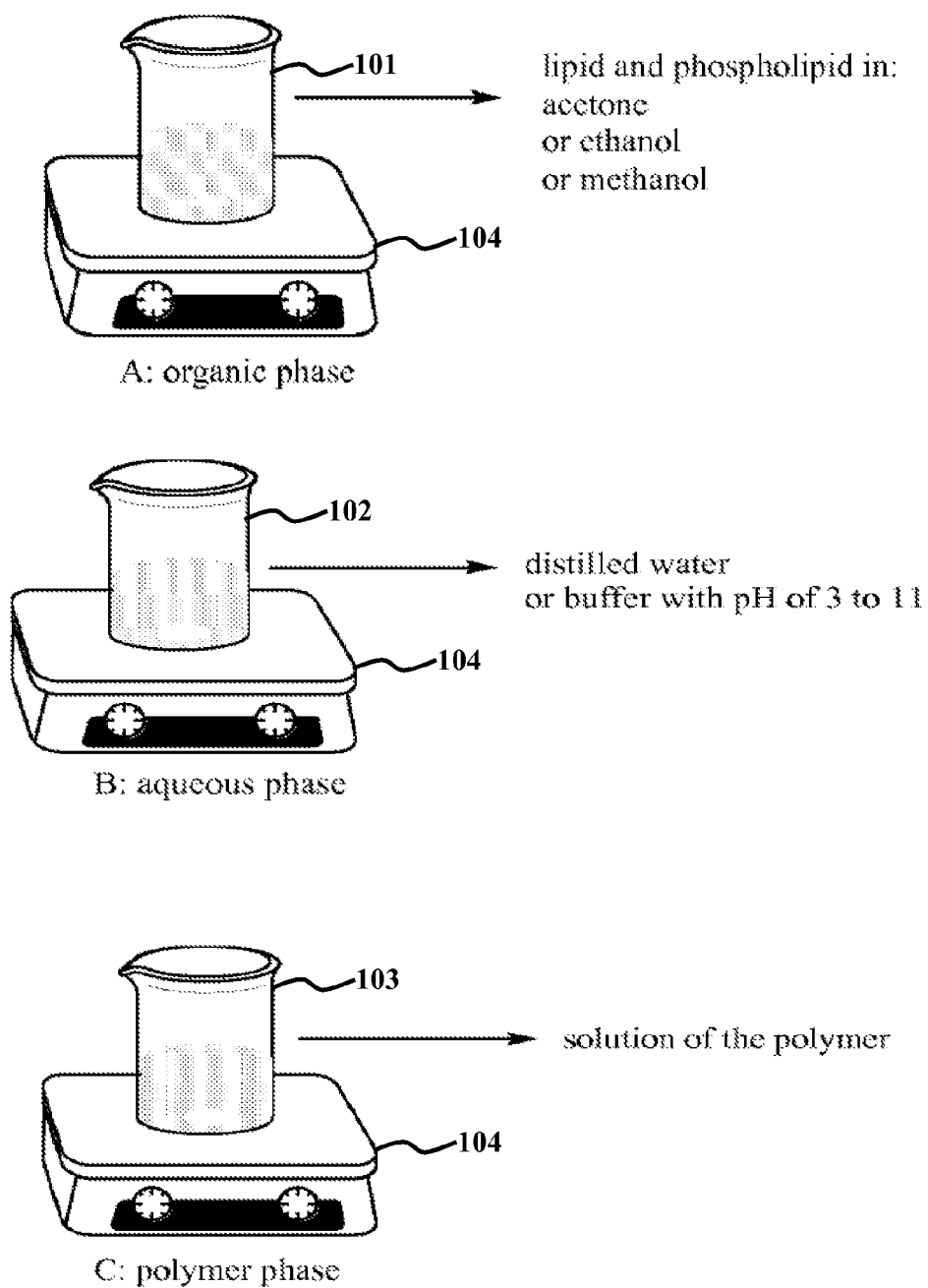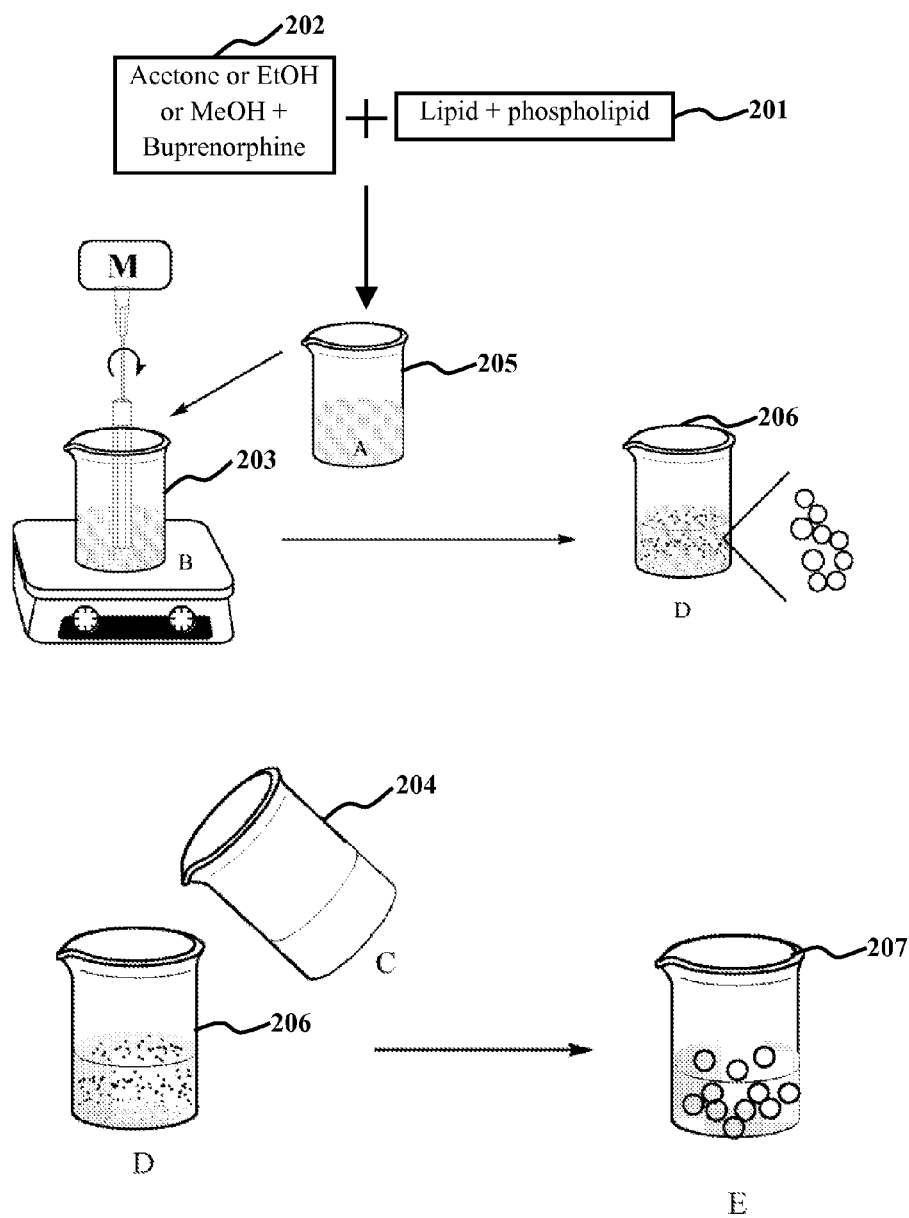
* cited by examiner

lipid and phospholipid in:
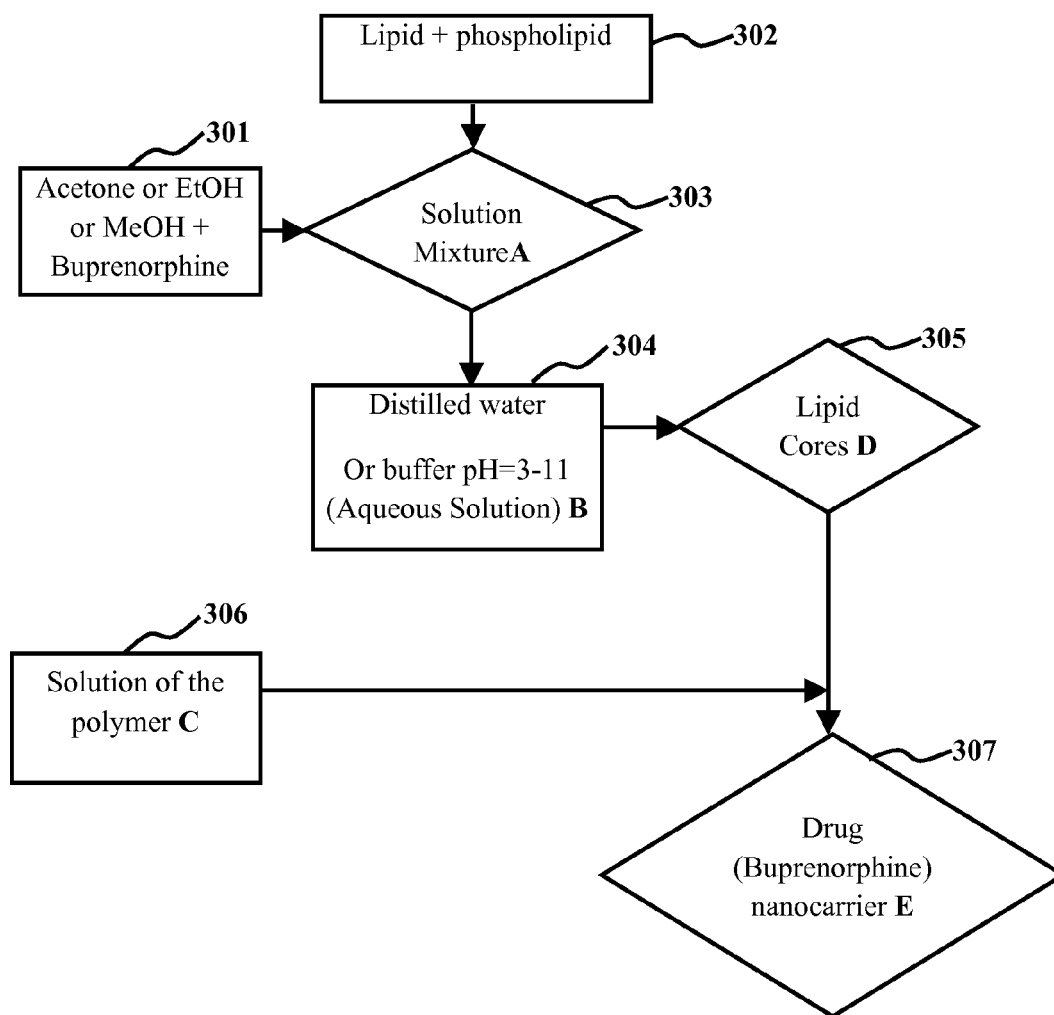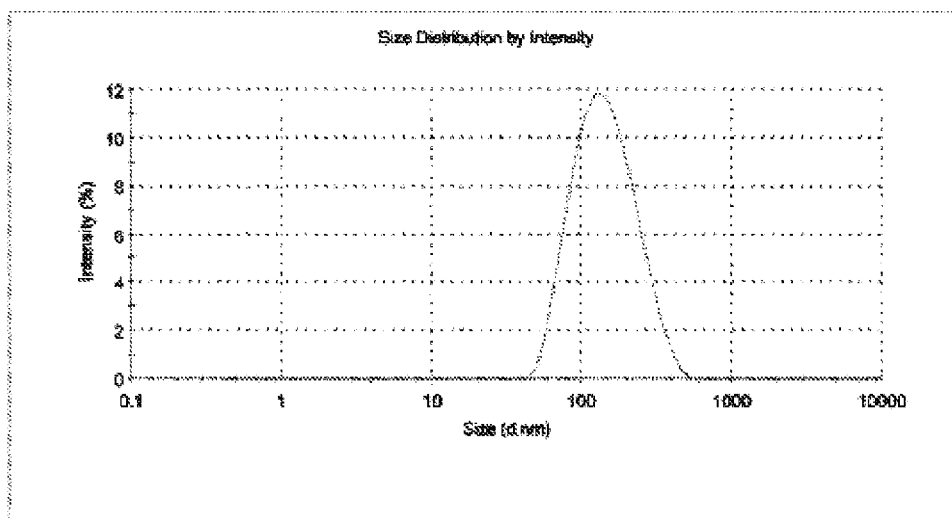acetone
or ethanol
or methanol

A: organic phase

distilled water
or buffer with pH of 3 to 11

B: aqueous phase

solution of the polymer

C: polymer phase

FIG. 1

FIG. 2

**FIG. 3**

## Size Distribution Report by Intensity
v2.1

Malvern

Results

|  |  |  | Size (d.nm): | % Intensity | Width (d.n... |
|---|---|---|---|---|---|
| Z-Average (d.nm): | 128.5 | Peak 1: | 155.2 | 100.0 | 74.56 |
| Pdi: | 0.160 | Peak 2: | 0.000 | 0.0 | 0.000 |
| Intercept: | 0.961 | Peak 3: | 0.000 | 0.0 | 0.000 |
| Result quality : | Good |  |  |  |  |



Size Distribution by Intensity

**FIG. 4**

## Zeta Potential Report

v2.2

Malvern Instruments Ltd - © Copyright 2005

### Results

|  | Mean (mV) | Area (%) | Width (mV) |
|---|---|---|---|
| Zeta Potential (mV): 22.8 | Peak 1: 22.8 | 100.0 | 4.71 |
| Zeta Deviation (mV): 4.71 | Peak 2: 0.00 | 0.0 | 0.00 |
| Conductivity (mS/cm): 0.139 | Peak 3: 0.00 | 0.0 | 0.00 |
| Result quality : Good |  |  |  |



Zeta Potential Distribution

FIG.5

**FIG.6**

705

703

704

702

701
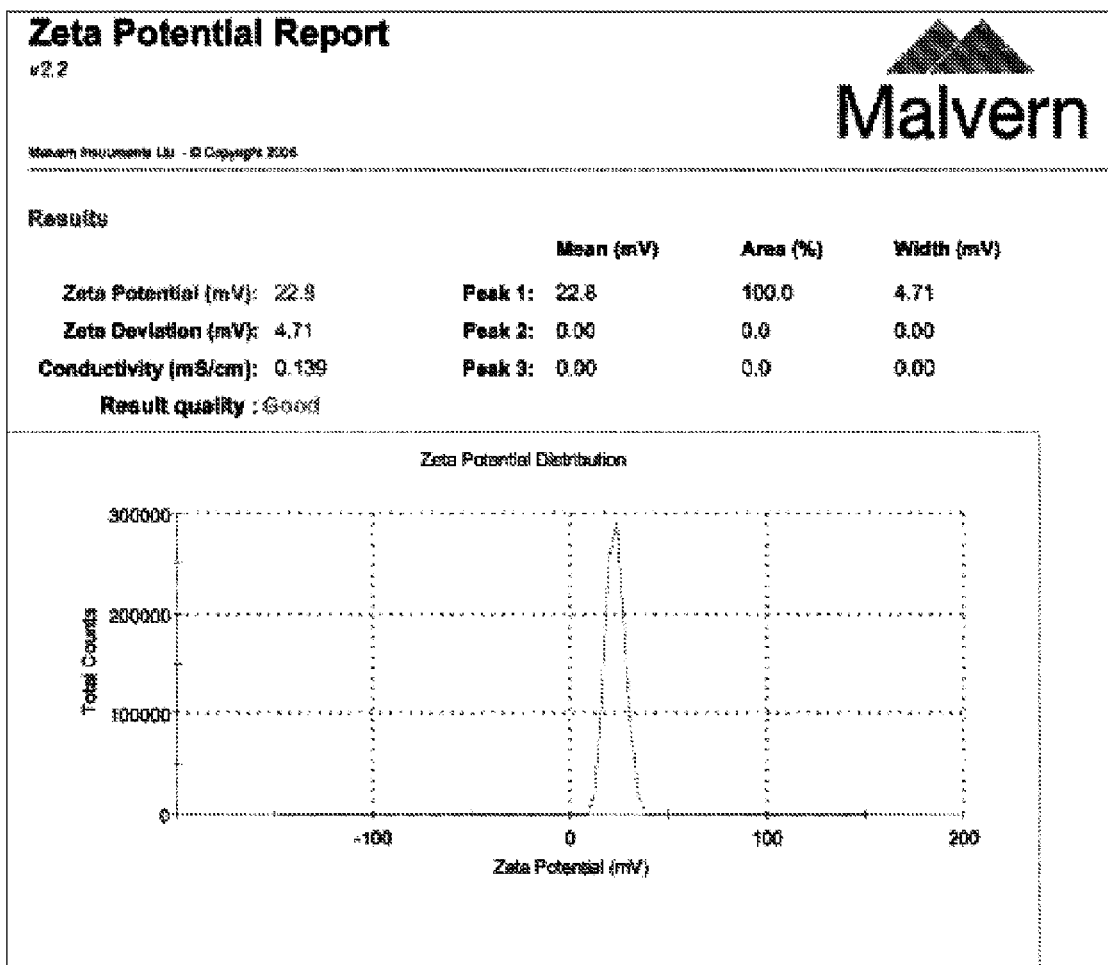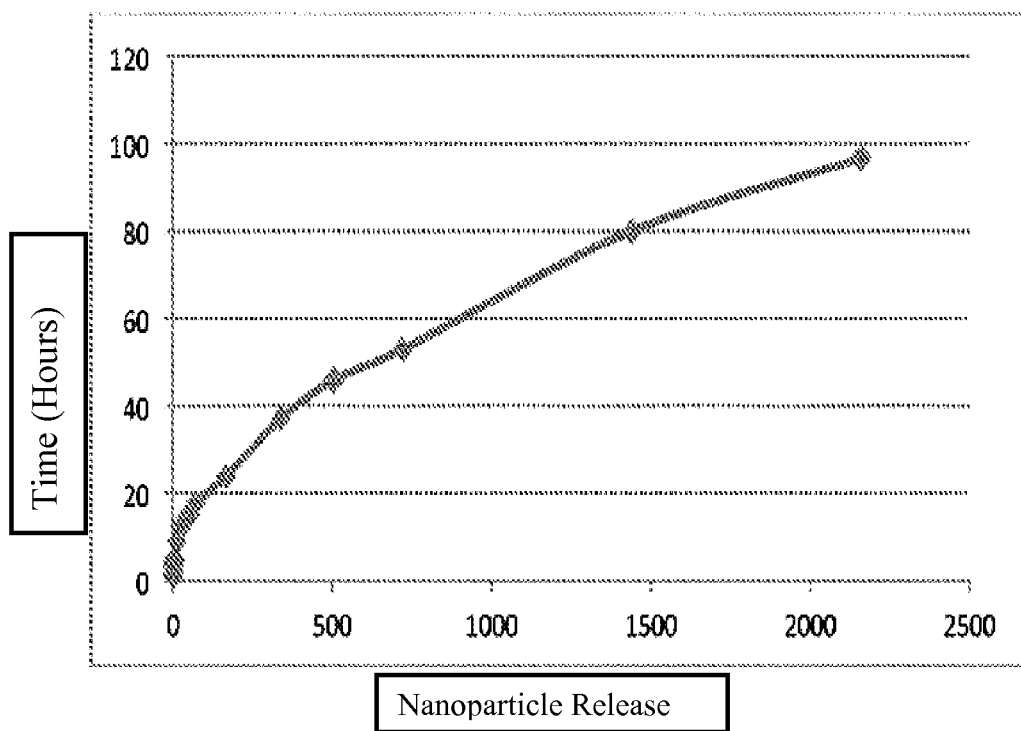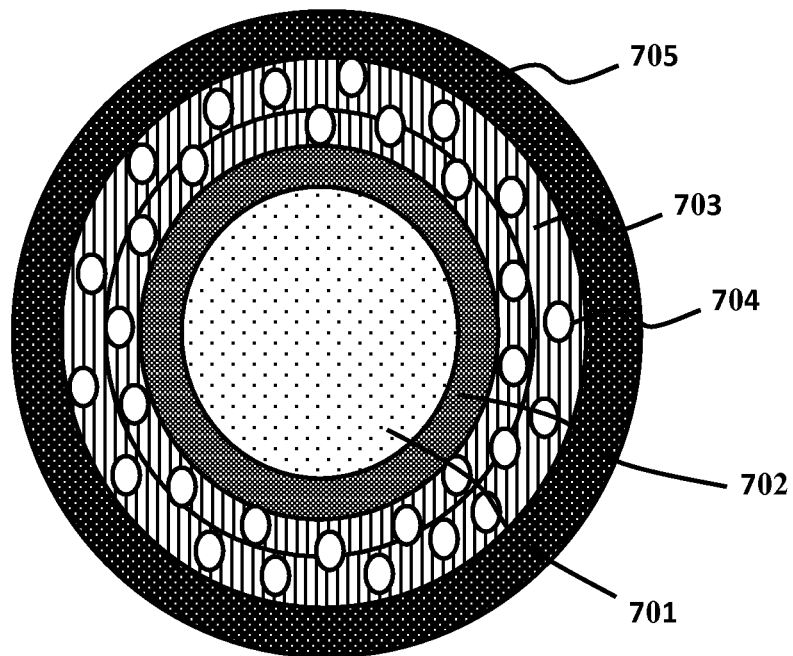
FIG.7

# METHOD AND SYSTEM FOR SYNTHESIZING NANOCARRIER BASED LONG ACTING DRUG DELIVERY SYSTEM FOR BUPRENORPHINE

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority of U.S. Provisional Patent Application No. 61/856,745, filed on Jul. 21, 2013, with the title, "Long-Acting Injectable Dosage Form Based on Nanotechnology for Buprenorphine", and the content of which is incorporated herein by reference in its entirely.

## BACKGROUND

### 1. Technical Field

The embodiments herein generally relate to the field of molecular nanotechnology. The embodiments herein particularly relate to nanomedicines or nanocarrier based drug delivery systems. The embodiments herein more particularly relate to a system and method for synthesizing long acting, and slow release nanoparticle or nano carrier based drug delivery system for Buprenorphine.

### 2. Description of the Related Art

In nanotechnology, a particle is defined as a small object that becomes a whole unit with respect to its transport and properties. The particles are further classified according to the diameter. The "nanoparticles" have a diameter within a range of 1 and 100 nanometer.

Nanotechnology has offered many advantages for novel drug delivery systems in terms of both time-controlled drug delivery and site-directed drug delivery. These advantages are mainly derived from the very small (submicron) sizes of the nanostructures used as nanocarriers for drugs as well as the possibility of engineering the carrier structure and/or surface according to the particular biological requirements.

"Nanomedicine" is the medical application of nanotechnology. Nanomedicine ranges from the medical applications of nonmaterial's to nano-electronic biosensor and even possible future applications of molecular nanotechnology.

The current problems for nano-medicine involve understanding the issues related to toxicity and the environmental impact on a nanoscale material.

The nano-medicine has provided the possibility of delivering drugs to specific cells using nanoparticles. The overall drug consumption and side effects are lowered significantly by depositing an active agent only in a morbid region at a required and appropriate dosage thereby eliminating a need for a higher dosage.

Drug delivery researchers are developing nanoscale particles or molecules to improve a "bioavailability" of a drug. The term bioavailability refers to the presence of drug molecules where they are used in the body and where they act against an ailment. Drug delivery system mainly focuses on maximizing the bioavailability both at specific places in the body and over a period of time.

The drug delivery systems such as lipid or polymer based nanoparticles are designed to improve the pharmacological and therapeutic properties of the drugs. Further, the metal based nanoparticles are also designed and developed to deliver the drugs.

The commonly used metals for nano-drug delivery system include but not limited to gold, silver, platinum etc. The metal based nanoparticles for the drug delivery system show toxicity. The recent studies in this arena have shown that positively charged gold nanoparticles are found to enter kidney, while

negatively charged gold nanoparticles remained in the liver and spleen. The positive surface charges of the nanoparticles decreases the rate of opsonization of nanoparticles in the liver, thereby affecting the excretory pathway. Even a relatively small size of the nanoparticles such as 5 nm can become compartmentalized in the perinephral tissues, and accumulate in the body over tissues. The advancement of research proves that targeting and distribution can be augmented by nanoparticles and the dangers of nano-toxicity have become an important question for the medical use in drug delivery.

A drug may cause tissue damage, but a drug delivery with regulated drug release can eliminate the problem. When a drug is removed too quickly from the body, this rapid drug delivery could force a patient to use a dose higher than a necessary dose. But a clearance can be reduced with drug delivery systems by altering the pharmacokinetics of the drug. A poor bio-distribution is a problem that can affect normal tissues through a widespread drug distribution, but the particulates from the drug delivery systems lower the volume of distribution and release the effect on a non-target tissue. The potential nano-drugs works by very specific and well understood mechanisms, one of the major impacts of nanotechnology and nano-science is the development of completely new drug delivery systems with more useful behaviors and less side effects.

Long-acting injectable drug delivery systems can benefit from the potentials of nanotechnology via the slow drug release from the nano-carriers already being loaded by the drug of interest. These drug carriers may be administered by injection into the host body through different routes mainly including intravenous, intramuscular, subcutaneous, intradermal, intra-arterial, intra-thechal, and intra-cardiac administration. Basically, a drug dose loaded in a nano-carrier is administered and the carrier, then supplies the drug needed for the particular pharmacological effect for a more extended time following a single dose compared to a conventional bolus dose. The pharmacokinetic outcome of the injectable long-acting dosage form is expected to be the lack of fluctuations in plasma concentrations of the drug which, eventually, results in avoiding the risks of over dosages, i.e., toxicity, or under dosages, i.e., treatment failure, in drug therapy. When a particular drug is administered in a chronic (long-term) basis in the form of repeated doses, a fluctuation in drug concentrations in plasma is observed. These pharmacokinetic fluctuations directly result in pharmacodynamic fluctuations where the drug affects the site of action and experiences peaks and troughs at the same time of concentration changes or after a lag phase. These fluctuations in the drug concentration are highly risky for patient, in particular for a drug like buprenorphine with narrow therapeutic index (small differences between therapeutic and toxic doses). With the conventional, currently available products of the drug in the market, there is always a risk for the patient to experience an overdosage (toxic effects in brain or other tissues) in the peak times or an underdosage (insufficient drug effect), both the stages are harmful for the patient.

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The patients are prescribed painkillers. An analgesic or painkiller is any member of the group of drugs used to achieve analgesia or relief from pain. The analgesic drugs act in various ways on the perinephral and central nervous systems. The analgesic include paracetamol (acetaminophen), the non-steroidal anti-inflammatory drugs such as the salicylates and opioid drugs such as morphine, oxycodone and buprenorphine.

The buprenorphine is a semi-synthetic partial opioid agonist that is used to treat opioid addiction in higher dosages, control moderate acute pain in non-opoid tolerant individuals in lower dosages and to control moderate chronic pain in even smaller doses. It is available in a variety of formulations such as tablets for moderate to severe pains, solutions for injections and transdermal preparations used for chronic pain.

The buprenorphine high dose leads to adverse drug reactions such as nausea and vomiting, drowsiness, dizziness, headache, memory loss, cognitive and neural inhibition, perspiration, itchiness, dry mouth, orthostatic hypotension, urinary retension and constipation etc. A proper dosage of the buprenorphine can minimize the risk of the side effects.

The buprenorphine is one of the most effective and most widely used narcotic analgesics. The analgesic drugs with well known indications in the relief of moderate to severe pains as well as the treatment of opoid dependence. The formulation of a long-acting product from buprenorphine has a potential to improve the patient outcome as well as the patient comfort so that the overall success of chronic therapy with this drug is resulted obviously from the achievement of a long time activity of the drug in vicinity of the site of action with a reasonable concentration. The lipid based as well as polymeric-based nanoparticles are prepared and loaded by the drug buprenorphine which serves as a drug reservoir capable of releasing the drug for long time periods in blood circulation, upon entry to the host body via injection. This long-term drug profile is used as a basis for prolonged chronic drug action toward the desired effects.

Hence there is a need to develop a nanoparticle based drug delivery system for buprenorphine without any threat of cytotoxicity. Also there is a need for a nanoparticle drug delivery system for buprenorphine to release the drug slowly and in a controlled manner to an action site. Further there is a need to develop a method for synthesizing the organic biomolecule based nanoparticle drug delivery system for buprenorphine.

The above mentioned shortcomings, disadvantages and problems are addressed herein and which will be understood by reading and studying the following specification.

## OBJECTIVES OF THE EMBODIMENTS

The primary objective of the embodiments herein is to synthesize a nano carrier based long acting drug delivery system for buprenorphine using a lipid core coated with a polymer.

Another objective of the embodiments herein is to synthesize the drug carrying nanoparticles or nanocarrier entrapping buprenorphine within the nanoparticles.

Yet another objective of the embodiments herein is to synthesize the drug nanocarrier based long acting drug delivery system for buprenorphine to provide a controlled release of the drug at a slow rate upon administration to an individual.

Yet another objective of the embodiments herein is to synthesize the drug nanocarrier based long acting drug delivery system for buprenorphine to enable an administration of a drug through intravenous, intramuscular, subcutaneous, intra-dermal, intra-arterial, intra-thecal and intra-cardiac routes.

Yet another objective of the embodiments herein is to synthesize the drug nanocarrier based long acting drug delivery system for buprenorphine by entrapping the drug using the anti-solvency effect of the aqueous matrix.

Yet another objective of the embodiment herein is to synthesize the drug nanocarrier based long acting drug delivery system for buprenorphine to cryoprotect the drug nanocarrier for future use and application.

These and other objects and advantages of the embodiments herein will become readily apparent from the following detailed description taken in conjunction with the accompanying drawings.

## SUMMARY

The various embodiments herein provide a system and a method for the synthesis of the nanocarrier based drug delivery for buprenorphine. The drug carrying nanoparticles or nanocarriers are prepared using a lipid/phospholipid core coated with a polymer. The nanocarriers entrap the buprenorphine drug for site directed drug delivery and slow release.

According to one embodiment herein, a method for synthesizing slow and controlled release of a buprenorphine entrapped in nanoparticle or nanocarrier is provided. The method comprises the steps of dissolving a buprenorphine in an organic solvent to get an organic solution. The buprenorphine is dissolved at a concentration of 0.1 to 10 mg/ml in the organic solvent. The organic solvent is 0.1 to 5 mg/ml. A phospholipid is added to the organic solution to form a bilayer around the buprenorphine. A lipid is added to the organic solution to obtain an organic solution mixture and the organic solution mixture comprises organic solvent with the buprenorphine, phospholipid and lipid. The organic solution mixture is added in dropwise to an aqueous solution to form a lipid core and the pH of the aqueous solution is in a range of 3-11. A volume ratio of the organic solution mixture to the aqueous solution is within a range of 0.05 to 3. A buffered solution of a polymer is added to the aqueous solution with a lipid core to form a coating layer around the lipid core to obtain a nano carrier. The pH of the polymer solution is in a range of 3.5 to 11. The polymer solution is added in dropwise to the aqueous solution in a volume ratio of 0.05 to 1.

The organic solvent is selected from a group consisting of a methanol, an ethanol, an acetone and an isopropanol. The phospholipid is selected from a group consisting of a phosphatidylcholine, a phosphatidylethanolamine, a phosphatidylinositol. The lipid is selected from a group consisting of a monostearyl glycerol, a distearyl glycerol, a palmitic acid, a stearic acid and a glyceryl stearate. The polymer is selected from a group consisting of a chitosan, a polyethylene glycol, a polyvinyl alcohol.

According to one embodiment herein, a system is provided for slow and controlled release of a buprenorphine entrapped in nanoparticle or nanocarrier. The system comprises a core of aqueous phase or solution, a lipid layer, a phospholipid bilayer with the buprenorphine and a polymer coating. The aqueous solution is made of water or a buffer. The phospholipid is selected from a group consisting of a phosphatidylcholine, a phosphatidylethanolamine, a phosphatidylinositol. The lipid is selected from a group consisting of a monostearyl glycerol, a distearyl glycerol, a palmitic acid, a stearic acid and a glyceryl stearate. The polymer is selected from a group consisting of a chitosan, a polyethylene glycol, a polyvinyl alcohol.

The buprenorphine is water-insoluble and presents in a phospholipid bilayer during a formation of a nanovesicle, and the buprenorphine gets loaded to the nanocarriers in a dissolved state within a thickness of the bilayers. The buprenorphine nanocarrier or nanoparticle particle size distribution curve exhibits a peak of 128.5 nm, and wherein buprenorphine nanocarrier has a relative low polydisparity index of 0.180. The buprenorphine nanocarrier or nanoparticle has a zeta potential within a range of 10 mv to 30 mv. The buprenorphine nanocarrier or nanoparticle has a zeta deviation of 4.71 mv. The buprenorphine nanocarriers or nanoparticles are

administered intravenously, intramuscularly, sub-cutaneously, intra-dermally, intra-arterially, intra-thecaly and intra-cardiac routes.

These and other aspects of the embodiments herein will be better appreciated and understood when considered in conjunction with the following description and the accompanying drawings. It should be understood, however, that the following descriptions, while indicating preferred embodiments and numerous specific details thereof, are given by way of illustration and not of limitation. Many changes and modifications may be made within the scope of the embodiments herein without departing from the spirit thereof, and the embodiments herein include all such modifications.

## BRIEF DESCRIPTION OF THE DRAWINGS

The other objects, features and advantages will occur to those skilled in the art from the following description of the preferred embodiment and the accompanying drawings in which:

FIG. 1 illustrates a schematic representation of the processes for the preparation of organic phase, aqueous phase and polymer phase solutions in the method for synthesizing a nano carrier based long acting drug delivery system for buprenorphine, according to an embodiment herein.

FIG. 2 illustrates a schematic representation of a method for synthesizing a nano carrier based long acting drug delivery system for buprenorphine, according to an embodiment herein.

FIG. 3 illustrates a flowchart indicating a method for synthesizing a nano carrier based long acting drug delivery system for buprenorphine, according to an embodiment herein.

FIG. 4 illustrates a graph indicating a size distribution profile of the drug nano-carriers for buprenorphine, according to an embodiment herein.

FIG. 5 illustrates a graph indicating the zeta potential distribution profile of the drug nano-carriers/nanoparticles for buprenorphine, according to one embodiment herein.

FIG. 6 illustrates a graph indicating the drug release profile of buprenorphine from a nano carrier based long acting drug delivery system for buprenorphine, according to one embodiment herein.

FIG. 7 illustrates a schematic structure of a nano carrier based long acting drug delivery system for buprenorphine, according to one embodiment herein.

Although the specific features of the embodiments herein are shown in some drawings and not in others. This is done for convenience only as each feature may be combined with any or all of the other features in accordance with the embodiments herein.

## DETAILED DESCRIPTION OF THE EMBODIMENTS

In the following detailed description, a reference is made to the accompanying drawings that form a part hereof, and in which the specific embodiments that may be practiced is shown by way of illustration. The embodiments are described in sufficient detail to enable those skilled in the art to practice the embodiments and it is to be understood that the logical, mechanical and other changes may be made without departing from the scope of the embodiments. The following detailed description is therefore not to be taken in a limiting sense.

The various embodiments herein provide a system and a method for the synthesis of the nanocarrier based drug delivery for buprenorphine. The drug carrying nanoparticles or

nanocarriers are prepared using a lipid/phospholipid core coated with a polymer. The nanocarriers entrap the buprenorphine drug for site directed drug delivery and slow release.

According to one embodiment herein, a method for synthesizing slow and controlled release of a buprenorphine entrapped in nanoparticle or nanocarrier is provided. The method comprises the steps of dissolving a buprenorphine in an organic solvent to get an organic solution. The buprenorphine is dissolved at a concentration of 0.1 to 10 mg/ml in the organic solvent. The organic solvent is 0.1 to 5 mg/ml. A phospholipid is added to the organic solution to form a bilayer around the buprenorphine. A lipid is added to the organic solution to obtain an organic solution mixture and the organic solution mixture comprises organic solvent with the buprenorphine, phospholipid and lipid. The organic solution mixture is added in dropwise to an aqueous solution to form a lipid core and the pH of the aqueous solution is in a range of 3-11. A volume ratio of the organic solution mixture to the aqueous solution is within a range of 0.05 to 3. A buffered solution of a polymer is added to the aqueous solution with a lipid core to form a coating layer around the lipid core to obtain a nano carrier. The pH of the polymer solution is in a range of 3.5 to 11. The polymer solution is added in dropwise to the aqueous solution in a volume ratio of 0.05 to 1.

The organic solvent is selected from a group consisting of a methanol, an ethanol, an acetone and an isopropanol. The phospholipid is selected from a group consisting of a phosphatidylcholine, a phosphatidylethanolamine, a phosphatidylinositol. The lipid is selected from a group consisting of a monostearyl glycerol, a distearyl glycerol, a palmitic acid, a stearic acid and a glyceryl stearate. The polymer is selected from a group consisting of a chitosan, a polyethylene glycol, a polyvinyl alcohol.
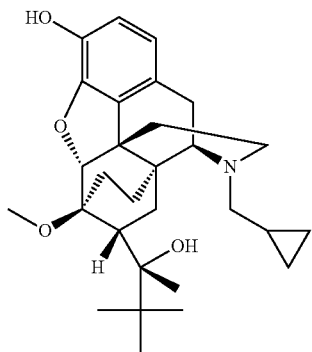
According to one embodiment herein, a system is provided for slow and controlled release of a buprenorphine entrapped in nanoparticle or nanocarrier. The system comprises a core of aqueous phase or solution, a lipid layer, a phospholipid bilayer with the buprenorphine and a polymer coating. The aqueous solution is made of water or a buffer. The phospholipid is selected from a group consisting of a phosphatidylcholine, a phosphatidylethanolamine, a phosphatidylinositol. The lipid is selected from a group consisting of a monostearyl glycerol, a distearyl glycerol, a palmitic acid, a stearic acid and a glyceryl stearate. The polymer is selected from a group consisting of a chitosan, a polyethylene glycol, a polyvinyl alcohol.

The buprenorphine is water-insoluble and presents in a phospholipid bilayer during a formation of a nanovesicle, and the buprenorphine gets loaded to the nanocarriers in a dissolved state within a thickness of the bilayers. The buprenorphine nanocarrier or nanoparticle particle size distribution curve exhibits a peak of 128.5 nm, and wherein buprenorphine nanocarrier has a relative low polydisparity index of 0.180. The buprenorphine nanocarrier or nanoparticle has a zeta potential within a range of 10 mv to 30 mv. The buprenorphine nanocarrier or nanoparticle has a zeta deviation of 4.71 mv. The buprenorphine nanocarriers or nanoparticles are administered intravenously, intramuscularly, sub-cutaneously, intra-dermally, intra-arterially, intra-thecaly and intra-cardiac routes.

According to an embodiment herein, the drug carrying nanoparticles are prepared using a lipid/phospholipid core which is then, coated by a polymer. The lipid part, stearic acid, lipoic acid, monostearin, distearin, and cholesterol are used in conjugation with phospholipid part which acts as the stabilizer for the solid lipid. As the phospholipid part, phosphatidyl choline (lecithin) and/or phosphatidyl ethanolamine

are used. The chitosan, alginate, poly (vinyl alcohol), poly (ethylene glycol), poly (vinyl pyrrolidone) are the polymers used in this process for coating.

According to one embodiment herein, buprenorphine is one of the most effective and most widely used narcotic analgesics. The buprenorphine is a semi-synthetic partial opioid agonist that is used to treat opioid addiction in higher dosages, to control moderate acute pain in non-opioid tolerant individuals in lower dosages and to control moderate chronic pain in even smaller doses. It is available in variety of formulations such as tablets, solution for injections and transdermal preparations used for chronic pain. The structure of the buprenorphine is shown below:



According to one embodiment herein, the first step in the process of synthesizing the buprenorphine drug nanocarriers is dissolving the lipid and phospholipid in an organic solvent. The organic solvent is chosen from a group comprising acetone, ethanol, and methanol. The concentration of the organic solvent is in the range of 0.1 to 5 mg/ml. The solution of lipid and phospholipid in an organic solvent is transferred into an aqueous phase consisting of distilled water or a buffer with pH of 3-11. The drug (buprenorphine) to be entrapped in the nanoparticles/nanocarriers is present in the aqueous phase at a concentration of 0.1 to 10 mg/ml. The volume ratio of organic-to-aqueous phase mixture is within a range of 0.05-3. The mixture obtained is mixed with a solution of the polymer. The polymer solution is prepared in a buffered medium with a pH range of 3.5 to 11.0. The polymer solution is added drop-wise to the organic-to-aqueous phase mixture in a volume ratio of 0.05 to 1.

According to an embodiment herein, the nanocarriers are capable of releasing the buprenorphine drug in a slow rate upon injection via intravenous, intramuscular, subcutaneous, intradermal, intrathecal and intracardiac routes.

According to one embodiment herein, the particle formation is achieved mechanistically by the diffusion (dilution) of the organic solvent within the aqueous host solvent to obtain the particles. The interested drug is entrapped in the nanoparticles/nanocarrier via the antisolvency effect of the aqueous matrix. The basis for the preparation of the phospholipid-based nanocarriers is a method known as "ethanol injection" with some modifications. In this method, the phospholipid, which is practically insoluble in water, is dissolved in a water-miscible solvent, typically ethanol. The ethanol is gradually added drop-wise to a higher amount of water (for example 10-times the ethanolic solution volume). When the phospholipid comes into contact with ethanol in the water phase, ethanol "diffuses" into the water phase and becomes diluted leading to formation of new solvent which is mainly water with a small portion of the ethanol. Since the phospholipid

cannot be dissolved in this new solvent and there is a vigorous shaking in system on the other hand, the amphiphilic phospholipids undergoes self-assemble process by using the vesicles made of phospholipid bilayers as their shells and an entrapped water phase as the core and the core is surrounded by the phospholipid bilayers. When a drug such as "buprenorphine", which is insoluble in water, presents itself in the medium at the time of nanovesicle formation, buprenorphine becomes loaded to the nanocarriers in a dissolved condition within the thickness of bilayers, as the only possibility for the buprenorphine to stay in this medium in a thermodynamic point of view, during the formation of the self assemblies because the drug is hydrophobic and cannot be found in any proportion within the core of the surrounding waters.

According to one embodiment herein, the nanocarrier is has a lipid-phospholipid-polymer structure each of the components offer a definite property to the drug delivery system. The lipid fraction makes the system a suitable carrier for lipiphilic drugs such as buprenorphine. The lipid fraction restricts the rapid release of the drug from the nanocarrier. The phospholipid component makes the system more amphiphillic to incorporate the lipophillic, the hydrophilic and the amphiphillic drugs. The presence of this phospholipid fraction offers the self assembly behaviour to the nanocarrier. The polymer forming a coating on the outer shell of the nanocarrier provides a surface charge, fluidity and mechanical strength.

According to one embodiment herein, the materials used for the synthesis of the drug nanocarriers/nanoparticles are divided into four groups. The four groups are organic solvents, phospholipids, lipids and polymers. The organic solvents which are used for the synthesis of the drug nanocarrier/nanoparticle are methanol, ethanol, acetone and isopropanol. The phospholipids which are used for the synthesis of the drug nanocarrier/nanoparticle are phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol. The lipids which are used for the synthesis of the drug nanocarrier/nanoparticle are monostearyl glycerol, distearyl glycerol, palmitic acid and stearic acid. The polymers which are used for the synthesis of the drug nanocarrier/nanoparticle are chitosan, polyethylene glycol, ad polyvinyl alcohol. The aqueous solution is a water or a buffer, which is used for the formation of the core.

According to one embodiment herein the drug such as buprenorphine in different concentrations is taken for the preparation of the drug carrying nanoparticles/nanocarriers based on specific objectives, therapeutic dosages and indications. The drug such as buprenorphine is then dissolved in organic solvent such as ethanol, methanol, or acetone to get a solution. The lipid (mainly a glyceryl stearate) is added in different amounts (quantities) to the solution of buprenorphine and organic solvent. The lipid is added in a specific concentration depending on the drug and organic solvent concentrations. This solution mixture consisting of drug (buprenorphine), organic solvent and lipid is added drop wise into an aqueous phase (water or buffer) to form the lipid cores. The buffered aqueous solution of the polymer with different concentrations is added dropwise onto the cores based on the amounts or quantities of other compounds present in the solution to form the coatings or shells around the phospholipid core.

According to one embodiment herein, the nanoparticle/nanocarriers are subjected to in-vitro characterization tests, after the synthesis of buprenorphine drug entrapped nanoparticle/nanocarriers.

According to one embodiment herein, the particle size distribution of the nano-dispersion is evaluated using the

Dynamic Light Scattering (DLS) method. The surface zeta potential of the nano-dispersion is also evaluated by the electrophoretic mobility method. The drug release profile of the nanoparticles is most important factor and is analyzed in vitro.

According to one embodiment herein, the synthesized drug loaded nanoparticle/nanocarrier is dried to form a powder using a freezer-dryer. The freeze-drying process enables the better storage. glucose, lactose, trehalose, sorbitol, glycerol, mannitol or Tween are used in a concentration of 0.25-5%, for cryopreservation, The characterization reveals an aqueous core with drug surrounded by a phospholipid bilayer. The lipid core is surrounded by the polymer shell. Two kinds of substances such as cryoprotectant and lyoprotectant are used for the cryopreservation by freeze-drying method of the drug loaded nanocarriers or nanoparticles. The role of cryoprotectant is to prevent irreversible aggregation of the nanoparticles during the freezing process. The cryoprotectant and lyoprotectant materials are mixed with the nanoparticles/nanocarriers (nano-dispersion) before drying. When the freezing process is carried out on the samples, the cryoprotectant and lyoprotectant materials provide either a physical barrier or an electrical barrier around each nanocarrier or align the particles in solid-liquid interfaces during the freezing process resulting in the protection of each individual carrier from being aggregated with the neighbouring particles. The lyoprotectants also play a similar role. The commonly used cryoprotectants and lyoprotectants are monosaccharides, disaccharides, polyols and non-ionic surfactants.

According to one embodiment herein, there are four mechanisms responsible for the drug release from a nanocarrier when administered to an individual. The mechanisms are passive diffusion, based on the Fickian kinetics, nanocarrier erosion occurring with time resulting in drug release, water penetration inside nanoparticles followed by channeling (the drug is dissolved and diffused based on the drug concentration gradient) and nanocarrier capture by the natural defense cells of the host body, then drug release out of the vehicle. These mechanisms contribute to the drug release from the nanocarrier.

FIG. 1 illustrates a schematic representation of the processes for the preparation of organic phase, aqueous phase and polymer phase solutions in the method for synthesizing a nano carrier based long acting drug delivery system for buprenorphine, according to an embodiment herein. A lipid and a phospholipid are dissolved in an organic solvent in a beaker. The organic solvent are selected from an acetone or an ethanol or a methanol (**101**). The lipid and phospholipid are dissolved in the organic solvent by a magnetic stirrer **104**. The drug such as buprenorphine is then dissolved in organic solvent such as ethanol, methanol, or acetone to get a solution (**101**). The lipid (mainly a glyceryl stearate) is added in different amounts (quantities) to the solution of buprenorphine and organic solvent. The lipid is added in a specific concentration depending on the drug and organic solvent concentrations. This solution mixture consisting of drug (buprenorphine), organic solvent and lipid is added drop wise into an aqueous phase (water or buffer) to form the lipid cores (**102**). The buffered aqueous solution of the polymer with different concentrations is added dropwise onto the cores based on the amounts or quantities of other compounds present in the solution to form the coatings or shells around the phospholipid core. Finally, a buffered aqueous solution of the polymer such as a poly cation with a pH of 3.5 to 11 and a concentrations based on the amount of other compounds is added dropwise onto the lipid cores to form the coats around the lipid cores (**103**) and the drug entrapped nanocarrier is

obtained. The polymer solution is added dropwise to the organic to aqueous phase in a volume ratio of 0.05 to 1. The buprenorphine is water insoluble and presents itself in the phospholipid bilayer.

FIG. 2 illustrates a schematic representation of a method for synthesizing a nano carrier based long acting drug delivery system for buprenorphine, according to an embodiment herein. The buprenorphine in different salts concentrations is taken based on the specific objectives, therapeutic dosages and indications. The buprenorphine is dissolved in an organic solvent, ethanol, methanol or acetone (**202**). The organic solvent has a concentration of 0.1 to 5 mg/ml. The drug such as buprenorphine is taken in the concentration of 0.1 to 10 mg/ml. Then different amounts of the phospholipid, mainly phosphatidylcholine, are dissolved in this solution and, finally, the lipid, mainly a glyceryl stearate, is dissolved in the same solution with a preset concentration depending on the drug and the organic solvent components (**201**). The mixing of organic solvent with buprenorphine, lipid and phospholipid yields a solution mixture-A (**205**). The solution-A is added dropwise onto an aqueous phase such as water or buffer with a pH in the range of 3-11 (**203**). The lipid cores-C are formed aqueous phase (**206**). The volume ratio of the organic to the aqueous phase mixtures is 0.05 to 3. Finally, a buffered aqueous solution of the polymer such as a poly cation with a pH of 3.5 to 11 with different concentrations, based on the amount of other compounds, is added dropwise onto the lipid cores to form the coats around the lipid cores (**204**) and the drug nanocarriers D are obtained (**207**). The polymer solution is added dropwise to the organic to aqueous phase in a volume ratio of 0.05 to 1. The buprenorphine is water insoluble and presents itself in the phospholipid bilayer.

FIG. 3 illustrates a flowchart indicating a method for synthesizing a nano carrier based long acting drug delivery system for buprenorphine, according to an embodiment herein, the lipid and the phospholipid are taken. The buprenorphine in different concentrations is taken based on the specific objectives, therapeutic dosages and indications. The buprenorphine is dissolved in an organic solvent, ethanol, methanol or acetone (**301**). The organic solvent has a concentration of 0.1 to 5 mg/ml. The buprenorphine to be entrapped is taken in the concentration of 0.1 to 10 mg/ml. Then different amounts of the phospholipid, mainly phosphatidylcholine, are dissolved in this solution and, finally, the lipid, mainly a glyceryl stearate, is dissolved in the same solution with a preset concentration depending on the drug and the organic solvent components (**302**). The mixing of organic solvent with buprenorphine, lipid and phospholipid yields a solution mixture-A (**303**). The solution-A is added dropwise onto an aqueous phase such as water or buffer with a pH in the range of 3-11 (**304**). The lipid cores-D are formed aqueous phase (**305**). The volume ratio of the organic to the aqueous phase mixtures is 0.05 to 3. Finally, a buffered aqueous solution of the polymer such as a poly cation with a pH of 3.5 to 11 with different concentrations, based on the amount of other compounds, is added dropwise onto the lipid cores to form the coats around the lipid cores (**306**) and the drug nanocarriers D are obtained (**307**). The polymer solution is added dropwise to the organic to aqueous phase in a volume ratio of 0.05 to 1. The buprenorphine is water insoluble and presents itself in the phospholipid bilayer.

EXAMPLE 1

Synthesis of Buprenorphine Carrying
Nanoparticle/Nanocarrier

The following materials are required for the synthesis of nano carrier based drug delivery system for buprenorphine.

1. Organic solvent: methanol, ethanol, acetone, isopropanol;

2. Phospholipids: Phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol;

3. Lipids: Monostearyl glycerol, Distearyl glycerol, Palmitic acid, Stearic acid

4. Polymers: chitosan, polyethylene glycol, polyvinyl alcohol.

Procedure:

In the first step based on the specific objectives, therapeutic dosages and indications the buprenorphine at different salts in different concentrations is taken. The buprenorphine is dissolved in an organic solvent, ethanol, methanol or acetone. The organic solvent has a concentration of 0.1 to 5 mg/ml. The buprenorphine to be entrapped is taken in the concentration of 0.1 to 10 mg/ml. Then different amounts of the phospholipid, mainly phosphatidylcholine, are dissolved in this solution and, finally, the lipid, mainly a glyceryl stearate, is dissolved in the same solution with a preset concentration depending on the drug and the organic solvent components. The mixing of organic solvent with buprenorphine, lipid and phospholipid yields a solution mixture-A. The solution-A is added dropwise onto an aqueous phase such as water or buffer with a pH in the range of 3-11. The lipid cores-C are formed aqueous phase. The volume ratio of the organic to the aqueous phase mixtures is 0.05 to 3. Finally, a buffered aqueous solution of the polymer such as a poly cation with a pH of 3.5 to 11 with different concentrations, based on the amount of other compounds, is added dropwise onto the lipid cores to form the coats around the lipid cores and the drug nanocarriers D are obtained. The polymer solution is added dropwise to the organic to aqueous phase in a volume ratio of 0.05 to 1. The buprenorphine is water insoluble and presents itself in the phospholipid bilayer.

FIG. 4 illustrates a graph indicating a size distribution profile of the drug nano-carriers for buprenorphine, according to an embodiment herein. With respect to FIG. 4, the particle size distribution of the nanoparticles is analyzed by DLS analysis. The curves in the graph of FIG. 4 are the long-normal probability curves. In the graph, log of the diameters of the nanoparticle populations is plotted against the relative contribution of the probability in the total number of particles based on the scattered light intensity from each sub-population. The particle size distribution curves in FIG. 4 exhibit only one peak (128.5 nm) with a relatively low polydispersity index (0.180). This indicates an ideal size of the nanoparticles with only one peak representing a unimodal size distribution.

FIG. 5 illustrates a graph indicating the zeta potential distribution profile of the drug nano-carriers/nanoparticles for buprenorphine, according to one embodiment herein. The zeta potential characterizes the electrical potential on the surface of a colloid. This parameter is of a particular importance both regarding the in vitro stability of the nanoparticles owing to the presence of a minimum electrical repulsion between the particles and also the in vivo fate of the nanocarrier upon entry to the host organism. The fate of the nanoparticles is regarding the effect of the surface potential on the capture of the nanoparticles by the natural defense mechanisms of the organism. The zeta potential required for the stability of the nanoparticles is 10 mv-30 mv. FIG. 5 shows the in vitro stability a potential of nanoparticles to be around 30 mv is ideal but not less than 10 mv. Also for the fate of the nanoparticles, a zeta potential between +30 mv and −30 mv is ideal, but the positive potential is the mostly preferred than neutral than negative, which is shown by the nanoparticles in FIG. 5. The FIG. 5 further illustrates the narrow distribution of the zeta potentials of the nanoparticles with a zeta deviation

of 4.71 mv, is a very promising result along with the unimodal distribution (only one peak) of the zeta potentials which is again promising with respect to the homogeneity of the particles.

FIG. 6 illustrates a graph indicating the drug release profile of buprenorphine from a nano carrier based long acting drug delivery system for buprenorphine, according to one embodiment herein. In FIG. 6, the gradual release of the drug with a near-constant (a straight line) release rate is observed as an ideal behaviour of a controlled release system. FIG. 6 further illustrates the absence of a significant burst of drug release in initial stages. Also the considerable high plateau time of 36 hours is highly promising for obtaining a slow drug release system upon injection to the host body.

According to one embodiment herein, the slow release and the controlled release of the buprenorphine is tested in vitro. 3 ml of the nanocarrier dispersion is poured to a dialysis sac with an atomic mass of 12 KDa. The dialysis sac is placed in 50 ml phosphate buffer saline solution (PBS) and is stirred gently at 20 rpm at 37° C. 1 ml aliquot sample is removed from the external medium at the start time (time 0) and at the predetermined time intervals and is replaced with fresh PBS. The drug concentration in the aliquot sample is determined with reference to a blank free drug solution placed at the same condition. The test reveals the slow and controlled release of buprenorphine from the nanocarrier or nanoparticle.

According to one embodiment herein, the buprenorphine nanocarrier or nanoparticles have many advantages i.e. in the preparation of the nanocarriers popularly available raw materials are used. Also a cost-effective and simple method is used for the preparation of nanocarriers. The biosafety of all the ingredients used in this process is well-accepted globally, as highlighted by their approval for human use by United States Food and Drug Administration (USFDA). The average size of the nanocarriers prepared makes them, on one hand, very suitable for avoidance of the biological capture by the body defense mechanisms and, on the other hand, provides a practically reliable space for being loaded by an adequate amount of the drug. The uniformly monodispersed particles provide a reproducible matrix to be loaded by the same amounts of the drug in different batches, a feature very important for the industrial production of the nanocarriers. The narrowly distributed positive electrical potential on the nanoparticles surfaces which offers a remarkable stability both in vitro and in vivo for the nanocarriers. The constant and slow rate of drug release from the nanoparticles, assures a long acting drug delivery system as intended by the investigators. The buprenorphine nanocarrier does not burst release the drug from the nanocarriers.

FIG. 7 illustrates a schematic structure of a nanocarrier based long acting drug delivery system for buprenorphine, according to one embodiment herein. The nanocarrier drug delivery system for buprenorphine comprises of an aqueous solution core 701. A lipid layer 702 is present/formed around the aqueous solution. A phospholipid bilayer 703 is present/formed around the lipid layer. The drug particles such as buprenorphine 704 are entrapped or embedded in the phospholipid bilayer. The outermost layer or coating of the buprenorphine drug nanocarrier is formed by a polymer 705. The organic solvent for dissolving the lipid and phospholipid is selected from a group consisting of a methanol, an ethanol, an acetone and an isopropanol. The aqueous solution is a water or a buffer, which forms the core. The phospholipid is selected from a group consisting of a phosphatidylcholine, a phosphatidylethanolamine, a phosphatidylinositol. The lipid is selected from a group consisting of a monostearyl glycerol, a distearyl glycerol, a palmitic acid, a stearic acid and a

glyceryl stearate. The polymer is selected from a group consisting of a chitosan, a polyethylene glycol, a polyvinyl alcohol.

The foregoing description of the specific embodiments will so fully reveal the general nature of the embodiments herein that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments.

It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. Therefore, while the embodiments herein have been described in terms of preferred embodiments, those skilled in the art will recognize that the embodiments herein can be practiced with modification within the spirit and scope of the appended claims.

Although the embodiments herein are described with various specific embodiments, it will be obvious for a person skilled in the art to practice the invention with modifications. However, all such modifications are deemed to be within the scope of the claims.

It is also to be understood that the following claims are intended to cover all of the generic and specific features of the embodiments described herein and all the statements of the

scope of the embodiments which as a matter of language might be said to fall there between.

What is claimed is:

1. A system for controlled release of buprenorphine which comprises nanoparticles comprising
   an aqueous core which is made of water or a buffer;
   monostearyl glycerol;
   a phospholipid bilayer comprising buprenorphine; and
   a chitosan coating forming an outermost layer,
   wherein the nanoparticle has a positive surface charge.

2. The system according to claim **1**, wherein the bilayer comprises a phospholipid selected from a group consisting of a phosphatidylcholine, a phosphatidylethanolamine, a phosphatidylinositol.

3. The system according to claim **1**, further comprising distearyl glycerol, palmitic acid, or stearic acid.

4. The system according to claim **1**, further comprising a polyethylene glycol or polyvinyl alcohol.

5. The system according to claim **1**, the nanoparticle size distribution curve exhibits a peak of 128.5 nm, and has a polydispersity index of 0.180.

6. The system according to claim **1** which can be administered in a manner selected from the group consisting of intravenously, intramuscularly, sub-cutaneously, intra-dermally, intra-arterially, through the intrathecal route, and through the intra-cardiac route.

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